# Radiation Therapy of Suprasellar Germ Cell Tumors

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A retrospective study was performed on 15 patients with suprasellar germ cell tumors treated by megavoltage external beam irradiation between Feb. 1979 and Dec. 1985. Follow-up period of survivors was 30 to 91 months. Histologic diagnosis was obtained before radiation therapy in 10 patients (9 germinomas and 1 mixed). Five patients were treated without histologic verification.

In 9 patients with biopsy-proven germinomas radiation therapy was delivered to the craniospinal axis in 6, to the whole brain in 3. In 5 patients with mixed germ cell tumor or elevated tumor marker, irradiation was delievered to the craniospinal axis in 2, to the whole brain in 2, and to the primary site only in 1. Total doses ranged from 5,000 to 5,500 cGy to the primary site, 3,000 to 4,400 cGy to the whole brain, and 1,300 to 3,000 cGy to the spine. In these 14, local tumor was controlled and primary or spinal failure was not observed. One patient without elevated tumor marker was treated to the whole brain. The tumor was not controlled and he had spinal recurrence. Overall survival and disease-free survival rates were 86% at 5 year.

It is proven that radiation therapy is an effective treatment for suprasellar germ cell tumors. The neuroendocrinologic presentation, tumor marker status, early response to radiation measured on CT seem to be useful means for selecting patients for radiation therapy when tissue diagnosis is not available.

Key Words: Suprasellar germ cell tumor, Radiation therapy

## INTRODUCTION

Tumors arising in the suprasellar region constitute an uncommon, biologically diverse group of primary brain tumors with varying radiosensitivity. Over 50% of tumors in this region are germinomas, highly radiosensitive and potentially radiocurable[1].

The radiocurability of suprasellar germinoma fostered by the report of Rubin and Kramer[2] has encouraged the use of radiation therapy, usually without biopsy. In verified germinomas computerized tomography (CT) has documented rapid tumor response, and these tumors often disappear with low doses of radiation ($\leq$2,000 cGy)[3~5]. This radioresponsiveness has been used as a therapeutic diagnosis of germinoma, thereby obviating the need for histologic confirmation for selected suprasellar tumors. Because of wide variety of cell types and heterogeneity in tumor behavior, coupled with the frequent lack of a histological diagnosis, controversies have persisted for the optimal management.

We analyzed 15 patients with a suprasellar germ cell tumor treated at Department of Therapeutic Radiology, Seoul National University Hospital between February 1979 and December 1985, and tried to find out the optimal approach for the management of suprasellar germ cell tumors.

## MATERIALS AND METHODS

From February 1979 to December 1985, 15 patients with suprasellar germ cell tumors received radiation therapy at the Department of Therapeutic Radiology, Seoul National University Hospital. Two patients had lesions involving both suprasellar and pineal regions (#7, #15 in Table 4 & 5). Minimum follow-up period of survivors was 30 months.

The patients ranged from 3 to 30 years of age, with the greatest number at the second decade (8/15). Male was predominant (2.8:1) (Table 1).

The most frequent complaint of patients was visual disturbance (8/15). Headache, associated with nause and vomiting, and polyuria/polydipsia were also among the first symptoms of the disease. Duration of symptoms ranged from 1 month to 8 years. In 67% of cases, symptoms were present for approximately 1 year prior to diagnosis. Diabetes insipitus was present in 47% of the cases. Precocious puberty, amenorrhea, growth retardation were present each in one patient. An additional

**Table 1.** Patient Distribution by Age and Sex

| | Male | Female | Total |
|---|---|---|---|
| ~ 5 | 1 | 0 | 1 |
| 6–10 | 3 | 1 | 4 |
| 11–15 | 4 | 2 | 6 |
| 16–20 | 2 | 0 | 2 |
| 21–25 | 0 | 1 | 1 |
| 26–30 | 1 | 0 | 1 |
| Total | 11 | 4 | 15 |

**Table 2.** Frequency of Presenting Symptoms

| Symptoms | No. of patients (%) | |
|---|---|---|
| Headache | 6 | (40) |
| Nausea, Vomiting | 6 | (40) |
| Visual difficulty | 8 | (53) |
| Polyuria, polydipsia | 7 | (47) |
| Mental disturbance | 2 | (13) |
| Growth retardation | 1 | ( 7) |
| Amenorrhea | 1 | ( 7) |
| Precocious puberty | 1 | ( 7) |
| Dysarthria | 1 | ( 7) |

**Table 3.** Frequency of Clinical Findings

| Clinical findings | No. of patients (%) | |
|---|---|---|
| Papilledema | 3 | (20) |
| Decreased visual acuity | 2 | (13) |
| Visual field defect | 6 | (40) |
| Paralysis of upward gaze | 2 | (13) |
| Transient hemiparesis | 5 | (33) |
| Facial palsy | 2 | (13) |

finding, noticed in 5 of our patients, was transient hemiparesis which is due to tumor involvement of basal ganglia (Table 2 and 3).

The cerebrospinal fluid was examined in 4 patients. But malignant cells were not found.

Ten tumors were verified histologically; these included 9 germinomas, 1 mixed germ cell tumor of embryonal carcinoma and choriocarcinoma (Table 4).

Tumor markers were studied in 10 patients; 4 from CSF and serum, 3 from CSF only and 3 from serum only. We used a radioimmunoassay kit of Serono Diagnostic SA for $\beta$-HCG (human chorionic gonadotropin) titer measurement and a product of ABBOTT for AFP (alpha-feto protein). In all 4 germinomas studied $\beta$-HCG titer was elevated. One mixed germ cell tumor patient showed elevation of both $\beta$-HCG and AFP. Of 5 patients with histologically unverified tumors $\beta$-HCG was elevated in 4 and AFP was marginally elevated in 1 (Table 4).

Five patients had surgical operations before radiation therapy; 1 underwent gross total removal of tumor, and 4 subtotal removal. Open biopsy of sterotaxic biopsy was perfomed in 4 patients. One patient had V-P shunt only (Table 4).

All patients were treated with Co-60 teletherapy equipment. One received radiation to the primary site only, 6 to the whole brain, and 8 to the entire craniospinal axis. After the initial whole brain irradiation, reduced field to the primary site was treated by two opposed lateral fields. The field size for the primary site ranged from 5×5 to 10 cm×10 cm, but in most it was 8 cm×8 cm. A posterior spinal cord field was matched to the whole brain field with a moving junction. Patients were usually treated five days per week with a daily tumor dose of 150 to 200 cGy. Total tumor doses ranged from 5,000 to 5,500 cGy. Spinal doses were 1,300 to 3,000 cGy. At present our policy for the treatment of patients with biopsy-proven germinoma, or positive cerebrospinal fluid (CSF) cytologic findings is craniospinal irradiation. The policy regarding treatment volume for other patients in whom no biopsy was performed is based on the tumor response as measured by serial CT during radiation therapy. The CT was performed after 2,000 cGy to the primary tumor and patients with excellent regression of tumor were considered to have radioresponsive germinomas. Because germinoma have a high likelihood of seeding along the craniospinal axis, the entire neuraxis was then treated. No patient received initial or adjuvant chemotherapy. Survival and disease-free survival data were calculated using the life table method.

## RESULTS

### 1. Confirmed Germinomas

Seven of 9 patients with biopsy-proven germinoma are alive 40 to 91 months from the date of

**Table 4.** Surgical Procedures, Pathology and Tumor Markers

| Pt. no. | Surgery | Pathology | Tumor markers CSF HCG | CSF AFP | serum HCG | serum AFP |
|---|---|---|---|---|---|---|
| 1 | Subtotal excision | Germinoma | – | – | – | – |
| 2 | Open biopay | Germinoma | – | – | – | – |
| 3 | Open biopsy | Germinoma | – | – | – | – |
| 4 | Stereotaxic biopsy | Germinoma | 12 | 11 | – | – |
| 5 | Subtotal excision | Germinoma | 96 | <5 | – | – |
| 6 | Subtotal excision | Germinoma | – | – | – | – |
| 7 | Subtotal excision | Germinoma | – | – | – | – |
| 8 | Stereotaxic biopsy | Germinoma | – | – | 260 | <5 |
| 9 | Subtotal excision | Germinome | 4500 | <7 | 3 | <5 |
| 10 | Total xecision | Mixed germ cell (embryonal+chorioca.) | – | – | 7200 | 680 |
| 11 | none | – | – | – | 24000 | 27 |
| 12 | none | – | 430 | <5 | 289 | <5 |
| 13 | none | – | 20 | <5 | – | – |
| 14 | none | – | 12.4 | <5 | 3 | 11 |
| 15 | V–P shunt only | – | 0 | <5 | <3 | <5 |

HCG= human chorionic gonadotropin (mIu/ml)
AFP = alpha-fetoprotein (ng/ml) : upper normal limit = 20ng/ml

**Table 5.** CT Response and Status by Patient Group

| Group | Pts. No. | RT field | Response* on CT | Follow-up (months)** |
|---|---|---|---|---|
| Germinoma | 1 | WB# | CR | 91 + NED |
| | 2 | WB | CR | 88 + NED |
| | 3 | CSA$ | CR | 68 + NED |
| | 4 | CSA | CR | 60 + NED |
| | 5 | CSA | CR | 1 + Lost NED |
| | 6 | WB | CR | 2 Died NED |
| | 7 | CSA | CR | 44 + NED |
| | 8 | CSA | CR | 42 + NED |
| | 9 | CSA | CR | 40 + NED |
| Nongerminomatous germ cell tumor or Marker positive | 10 | CSA | CR | 37 + NED |
| | 11 | primary | NR | 49 + NED |
| | 12 | WB | NR | 30 + NED |
| | 13 | CSA | CR | 59 + NED |
| | 14 | WB | PR | 48 + NED |
| No biopsy and marker negative | 15 | WB | NR | 16 DOD*** |

* CR : Complete response
NR : No response
PR : Partial response
# WB : Whole brain

** NED : No evidence of disease
*** DOD : Died of disease
$ CSA : Craniospinal axis

surgery. In all 9 patients tumor disappeared completely on CT at the completion of radiation therapy. Six patients received craniospinal irradiation. Five of these are alive 40 to 68 months without evidence of disease and 1 patients were lost at 1 month without evidence of disease.

Three patients did not receive spinal irradiation. One patients did not receive spinal irradiation because of poor performance status and died 2 month after the completion of radiation therapy due to complication of diabetes insipidus. Remaining 2 patients are alive 88 and 91 months without evidene of disease (Table 5, 6).

### 2. Confirmed Nongerminomatous Germ Cell Tumor or Elevated Tumor Marker

All 5 patients are alive 30 to 59 months from the date of initiation of radiation therapy. One patient with mixed germ cell tumor (embryonal carcinoma and choriocarcinoma) was treated with craniospinal irradiation after total removal of tumor. This patient is alive 37 months without evidence of disease. In the remaining four patients with elevated $\beta$-HCG level, irradiation was delivered to the craniospinal axis in 1, to the whole brain in 2, and to the primary site in 1. There were little change on CT at the completion of radiation therapy but $\beta$-HCG level declined (Table 5, 6).

### 3. Histologically Unproven and Negative Tumor Marker

Only one patient was included in this group. This patient received V-P shunt before irradiation. There was little change on CT at completion of radiation therapy, and spinal irradiation was not delivered. After 10 months, however, he had spinal recurrence, and received radiation therapy to the spine. He died 5 month thereafter (Table 5, 6).

In total, local tumor control was achieved in 93 % (14/15). Overall 5-year and disease-free survival was 86% (Fig. 1).

## DISCUSSION

Tumors of the pineal and suprasellar regions account for only 0.4 to 1% of all intracranial neoplasms in Western[6] and 4% in Japan[7].

Tumors arising in these areas may be classified into four histogenetic groups: 1) tumors of germ-cell origin, 2) tumors of pineal parenchymal cell origin, 3) tumors originating from glial or other surrounding tissues and 4) non-neoplastic cysts and vasular lesions[1]. The incidence of germ cell neoplasms is considered to account for more than 50% of tumors in this location. The etiology of germinal malignancies is unknown. In Japan and Taiwan, germ cell tumors comprise 2.1% to 9.4% of primary intracranial neoplasms. This is consistently higher than 0.4% to 3.4% reported in Western series. Ninety-five percent of primary intracranial germ cell tumors originate in the region of the third ventricle along an axis from the suprasellar cistern (37%) to the pineal gland (48%)[1,8]. Involvement of both sites, either sequentially or simultaneously, occurs rarely (6%), as does origin within the third ventricle (3%), basal ganglia-thalamus (3%) or other ventricular sites (3%). Germinomas preferentially (57%, including patients with multicentric involvement) involve the suprasellar region, while 68% of nongerminomatous germ cell tumors arise in the pineal gland. The germ cell tumors arising within the basal ganglia-thalamus are all germinomas[8~11].

From February 1979 to December 1985 we had experienced 32 cases with tumors of the pineal and suprasellar regions excluding confirmed non germ cell tumors; 13 suprasellar (including parasellar), 27 pineal, 2 both sites. Of 15 cases of suprasellar

**Table 6.** Failure Pattern by Patient Group

| Group | Total | LF* | SF** | DF*** | NED |
|---|---|---|---|---|---|
| Germinoma | 9 | 0 | 0 | 0 | 7 |
| NG–GCT or marker positive | 5 | 0 | 0 | 0 | 5 |
| No biopsy and marker negative | 1 | (1) | 1 | 0 | 0 |

* LF : Local failure
** SF : Spinal failure
*** DF : Distant failure
NG–GCT : Nongerminomatous germ cell tumor

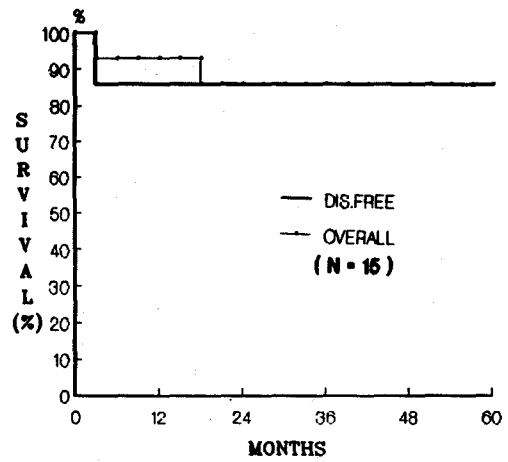


**Fig. 1.** Supra: ilar germ cell tumor : Actuarial overall and disease-free survival (N=15).

tumor (including 2 both sites) 9 cases were histologically comfirmed germinomas and one case was mixed germ cell tumor (embryonal carcinoma and choriocarcinoma). During the same period there were 306 primary intracranial tumors in our hospital; verified germ cell tumors comprise 3.7%, and this is compatible with those of Oriental series.

Initial surgical management of pineal region tumors is difficult to achieve because of their location and infiltrative nature. Historically a high mortality rate (30% to 50%)[12~15] was associated with surgical exploration; frequently, this led to the use of radiotherapy without biopsy proof of the nature of the lesion and decompressive shunting was performed if necessary[6,16~22]. Recently, however, neurosurgical advances have decreased the operative mortality[23,24] and many patients, particularly those with suprasellar lesions, now have a histological diagnosis at the time of referral for radiotherapy.

In the patient presenting with visual symptoms, diabetes insipidus, and a mass in the suprasellar area, the diagnosis of germinoma must be suspected. Intracranial germinal malignancies result, if untreated, in progressive endocrine and neurologic dysfunction and finally death. Even with appropriate radiotherapy, preexisting deficits such as visual field defects and diabetes insipidus are only rarely reversed, although tumor progression and its consequences are certainly stopped. For these reasons, early diagnosis and treatment of this tumor are crucial. The neuroradiologic[25] and pathologic diagnosis[26] of germinoma is very accurate. The introduction of CT has improved neurodiagnosis and easily permits the serial assessment of the tumor size and response to radiation therapy[3~5].

Advantage may be taken of the production of marker substances in blood and CSF by certain germ cell tumors, not only for diagnosis (thereby avoiding a hazardous surgical approach and biopsy of suprasellar tumors) but also for monitoring treatment response and detecting early tumor recurrence.

Germinomas may infiltrate, spread along the ventricular walls, or seed throughout the leptomeninges. The incidence reported for positive spinal fluid cytologic findings in patients with germinoma varies from 9%~10% to 20%~30% and this may reflect differences in the methods of detection and fluid sampling[27]. In a large series of patients with biopsy-proven germinoma, the incidence of cytologically positive ventricular fluid was 85%, but in this same group only 55% had positive spinal fluid[28]. Sung et al[21] reported metastasis to the cerebrospinal subarachnoid space in 57% (8/14) of histologically verified germinomas. This is at variance with some reports showing an approximate 10% nonactuarial failure rate in the spinal canal after local irradiation only. It is clear that opinions vary regarding the risk of tumor seeding and the need for routine craniospinal irradiation[19,22,29]. Some authors insist that in the absence of a biopsy, the incidence of spinal seeding is low and does not warrant routine spinal irradiation[15,30,31]. With the more widespread use of preradiotherapy biopsy there has been an increase in the incidence of seeding of the subarachnoid space[21,24,29]. The increased incidence of spinal subarachnoic seeding in patients who have had surgical interventions may necessitate craniospinal axis irradiation. Some authors insist routine craniospinal axis irradiation for all patients with proven or suspected germinomas, if the maximum number of long-term survivors is to be achieved[27].

In our study 10 patients have had surgical interventions (except 1 V-P only) and among them 3 patients (including one nongerminomatous germ cell tumors) did not receive spinal irradiation. However. any spinal failure was not observed in 2 patients with a follow-up of 88 and 91 months respectvely. PreRT CSF studies were not available in these 3 cases. Despite of these results we do not think that craniospinal axis irradiation is not necessary for patients with germinomas. More accumulation of treatment results is needed for this problem. And we think that it is necessey to find out various factors requiring spinal irradiation to exclude overtreatment. At present our policy is to irradiate craniospinal axis in patients with proven or suspected germinomas.

In our study 8 patients received spinal irradiation with doses of 1,300 to 3,000 cGy. Spinal failure was not observed in 7 patients with a follow-up of 37 to 68 months except one patient lost to follow up. Among them 2 patients were in nongerminomatous germ cell tumor or marker positive group. They showed excellent response of primary tumor on CT, so received spinal irradiation. Because CSF cytology studies were not available in all patients it is diffcult to induce optimal dose for spinal irradiation from this study. But we believe that dose of 2,000 to 2,500 cGy is adequate in cases of negative cytology studies. At present we use dose of 2,400 cGy for patients with negative cytologic examination of CSF. This dose causes minimal growth retardation in the spine of growing children[32,33].

Higher dose of radiation (3,600 cGy) is used if neoplastic cells are found in the CSF. Previously reported 5-year survival rates of 56% to 88%[7,9,22,29] after irradiation to only the primary tumor and ventricles are mostly lower than our survival rate of 86%. Although the results for neuraxis irradiation appear better, they are not significantly different from those for local irradiation only. Because of the infiltrating nature of germinomas, the tendency toward intraventricular spread, and the high incidence of intracranial recurrence, the use of fields encompassing at least the entire ventricular system[22,34], or the whole brain[6,15,24,27,30] is generally recommended.

It is our policy to irradiate whole brain with doses of at least 3,600 cGy in cases of germinoma. We have not experienced intracranial recurrence as yet. Because of the extreme radiosensitivity of germinoma and the fact that 3,000 cGy is sufficient to eradicate nodal metastases from testicular seminoma, the policy to prescribing doses of 5,000 cGy or higher for intracranial germinoma may be questioned[6,22]. However, it is evident that doses of 5,000 to 5,500 cGy are required to ensure total eradication of primary site. The intracranial recurrence rate in patients receiving 5,000 cGy or higher to the primary tumor site is substantially less than in those receiving less than 5,000 cGy[15,21]. This is because some "germinomas" contain yolk-sac or other less radiosensitive elements and require a higher dose[27]. In our study, of eight patients with proven germinomas elevated $\beta$-HCG titers were observed in 4. All patients showed excellent response on CT with doses of 5,000~5,500 cGy. It is controversial whether $\beta$-HCG production by a germinoma alters the patient's prognosis[35]. The presence of these biomarkers has been shown to be a grave prognostic sign in patients with testicular germ cell tumors[36,37] and may be for those with intracranial germinal malignancies as well. Five patients with nongerminomatous germ cell tumor or marker positive received doses of 5,000 cGy to the primary site and are alive without evidence of disease with a follow up of 37 to 59 months. More than 5,500 cGy is not thought to be rewarding even for those less radio-responsive tumors. CT taken at the completion of radiation therapy revealed no response in 2 and partial response in 1 patient. It seems that nongerminomatous germ cell tumors respond more slowly to radiation.

Patients with germinoma treated by surgical excision and postoperative radiation therapy do not appear to do better than those treated with radiation therapy alone[21,38]. Combined surgery and radiation therapy in one large series has an overall survival rate of 75% at 5 years; in other series the 5-year survival rate for germinomas on which biopsy had been performed and were treated by radiation alone is 79% to 88%[6,22,29]. These comparable data support the idea that surgery for histolgic verification or for resection of germinoma is not necessary. In our study no survival difference was observed between two groups. It can be suggested that a reasonable treatment of a patient with a solitary tumor in the suprasellar area, and without endocrine or tumor marker abnormalities, is a therapeutic trial of radiation therapy with 2,000 to 3,000 cGy followed by reassessment with CT. If there is no tumor regression then biopsy (if technically and clinically feasidle) may provide histologic information that can guide further therapeutic decisions.

The high effectiveness of chemotherapy for testicular germ cell tumors can be applied to tumors of the same type lying intracranially adjunctively or at relapse[11,39]. A recent report suggested that neoadjuvant chemotherapy could reduce radiation dose without compromising long-term survival, thereby allowing a reduction of some of the late effects of therapeutic radiation[40]. However, the optimum management must be determined in the context of controlled, randomized clinical trials conducted by large cooperative groups.

In summary, radiation therapy is an effective treatment for suprasellar germinomas whether tissue diagnosis has been confirmed or not. Serial CT and immunochemical analysis of the blood and CSF can aid in the assessment and guide treatment. In some patients biopsy or subtotal excision may aid in selecting appropriate therapy (further radiation therapy and/or chemotherapy) for patients with tumors not responding to initial radiation therapy.

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═ 국문초록 ═

## 뇌하수체상부 배아세포종의 방사선치료 성적

서울대학교 의과대학 치료방사선과학교실

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1979년부터 1985년까지 서울대학교병원 치료방사선과에서 외부 방사선조사를 시행한 15명의 뇌하수체상부 배아세포종(전이송과선종) 환자에 대한 후향적 분석을 시행하였다. 생존자의 추적기간은 30~91개월이었다.

10명의 환자는 방사선치료전 조직학적으로 진단되었으며 나머지 5명은 조직학적 진단이 없이 방사선치료를 시행하였다. 조직학적으로 진단된 9명중 배아세포종 환자 6명은 전뇌와 척추에 3명은 전뇌조사를 시행하였다. 혼합 배아세포종 및 종양 marker 양성인 5명의 환자중 2명은 전뇌, 그리고 1명은 원발병소 부위에만 방사선치료를 시행하였다. 총 방사선량은 원발병소에 5,000~5,500 cGy, 전뇌에 3,000~4,400 cGy 그리고 척추에 1,300~3,000 cGy였다. 상기 그룹 14명의 환자에서 원발병소는 완전 관해 되었으며 척추실패는 관찰되지 않았다. 조직학적 진단이 없고 marker의 상승이 없었던 한 환자에서 전뇌 방사선조사를 시행하였으나 원발병소의 완전관해 없이 척추 재발이 발생하였다. 방사선치료는 뇌하수체상부 배아세포종에 유효한 치료방법이며 신경 내분비학적 양상과 함께 조직학적 진단이 불가능한 경우에 있어서 소량의 방사선치료 후 관해정도 관찰은 이후의 치료방향설정에 유용한 수단으로 이용될 수 있다.